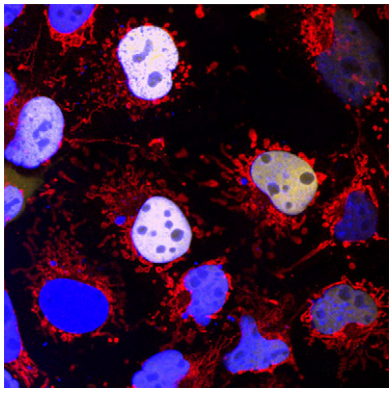
Molecular Medicine Select

Cell

The increasing prevalence of obesity and its negative impact on overall health have promoted the study of factors, both genetic and environmental, that control weight gain. This issue's Select discusses recent studies that analyze the function of obesity-related genes and our complex response to food intake.

Obesity Jumps on the Demethylase Bandwagon



FTO (yellow and white) localizes to the nucleus (blue) of the cell. Image courtesy of C. Schofield.

Recently, genome-wide association studies have linked variations in alleles of the *FTO* (fat mass and obesity associated) gene to obesity. Gerken et al. (2007) now reveal that *FTO* encodes a nucleic acid demethylase. Upon examination of the sequence of FTO, the authors noticed a domain that had homology to 2-oxoglutarate oxygenases. These enzymes are involved in a variety of processes including DNA repair and histone lysine demethylation. The authors expressed and purified murine *Fto* from bacteria and demonstrated that it displayed the enzymatic activity of a 2-oxoglutarate oxygenase. To identify potential substrates of FTO, the authors investigated whether FTO could act on the substrates of other 2-oxoglutarate oxygenases. This analysis revealed that FTO could remove methyl groups from methylated single-stranded DNA and that this enzyme had a preference for 3-methylthymine as a methylated substrate. Interestingly, *FTO* single nucleotide polymorphisms that are linked to obesity are in the introns of the *FTO* gene and may affect expression of *FTO* mRNA. The authors examined the expression pattern of *Fto* mRNA in mice and found that it is highly enriched in the hypothalamus, a site in the brain that is important for regulating energy balance. Gerken et al. then examined the amounts of *Fto* mRNA in the hypothalamus of mice that were deprived of food. In the arcuate nucleus of the hypothalamus, *Fto* mRNA was decreased by 60% in mice that were fasting, indicating that levels of *Fto* mRNA fluctuate with nutritional status. The next steps are to determine whether FTO is involved in nucleic acid demethylation or in DNA repair in vivo and how its enzymatic activity impinges on metabolism. Perhaps FTO specifically regulates the transcription of genes involved in metabolism through demethylation. Analysis of the effects of *Fto* mutations on the demethylase activity of the enzyme and on obesity in mice should be informative.

T. Gerken et al. (2007). Science. Published online November 8, 2007. 10.1126/science.1151710.

How a Gut Hormone Affects your Brain

The enhancement of brain activity (red) in the orbital frontal cortex in response to PYY. Image courtesy of R. Batterham.

Understanding the regulation of human feeding behavior requires insights into the contribution of a variety of factors including emotion and reward. Batterham et al. (2007) set out to determine how the gut hormone peptide YY_{3-36} (PYY)—which is released in the gut after a meal and is thought to mediate the feeling of satiety—affects feeding behavior in humans. Using whole-brain blood-oxygen-dependent (BOLD) functional magnetic resonance imaging (fMRI) Batterham et al. imaged the active regions of the brains of eight food-deprived humans who were administered PYY intravenously. Each person was subjected to 100 min of continuous fMRI in which saline was administered for the first 10 min followed by 90 min of either saline or PYY. The subjects were blinded to the study condition and were in an environment deprived of sensory cues to negate the effects of food-related stimuli. The investigators then measured the caloric intake of the subjects during a test meal 30 min after the termination of imaging. The caloric intake of all subjects was reduced by PYY. They then examined regions of the brain that were active when PYY was administered. Regions of the hypothalamus and brainstem were activated, but the greatest activation was in the left caudolateral orbital frontal cortex (OFC) that has been implicated in processing reward. They were also able to show that when PYY levels were low, the activity in the hypothalamus could predict subsequent feeding behavior. However, when PYY levels were high, the activity of the OFC predicted subsequent feeding behavior. Thus, brain activity that predicts calorie intake switches from the hypothalamus to the OFC in response to PYY. Furthermore, a single gut hormone can alter the activity in the OFC in the absence of food-related sensory cues. These data also indicate that the rewarding aspects of food are diminished through modulation of OFC activity by PYY. Increased understanding of these complex regulatory circuits could help in the development of better treatments to fight obesity.

*R.L. Batterham et al. (2007). Nature **450**, 106–109. Published online October 14, 2007. 10.1038/nature.06212.*

Stay away from JNK

Obese individuals often develop insulin resistance that contributes to type II diabetes. Recent studies have shown that obesity is associated with chronic low-grade inflammatory responses that activate protein kinases, such as the Jun kinases (JNKs), contributing to the development of type II diabetes. Remarkably, *Jnk1*-deficient mice remain lean and are resistant to diet-induced obesity. In fact, when fed a high-fat diet, these mice exhibit reduced expression of proinflammatory cytokines. To dissect the function of JNK1 in obesity, Solinas et al. (2007) engineered mice that lacked *Jnk1* specifically in their hematopoietic or nonhematopoietic compartments. This was accomplished by adoptively transferring wild-type or *Jnk1*-deficient bone marrow cells into lethally irradiated *Jnk1*-deficient or wild-type mice, respectively. Using these mice, Solinas et al. discovered that the resistance to diet-induced obesity observed in JNK1-deficient mice is specifically due to JNK1 deficiency in nonhematopoietic compartments. These mice expend more energy and are leaner than their wild-type counterparts. Next the author examined Jnk1 deficiency in hematopoietic compartments and found a decrease in insulin resistance due to a reduction in obesity-induced inflammation due to impaired proinflammatory cytokine expression by adipose tissue macrophages and Kupffer cells lacking *Jnk1*. This study nicely dissects the specific contribution of JNK1 in different compartments to obesity-induced insulin resistance and should help inform the design of better therapeutic interventions for treating obesity.
G. Solinas et al. (2007). Cell Metab. ***6****, 386–397.*

A New Player in Lipid Absorption

To determine the physiological function of the transcription factor PlagL2 that has been implicated in human acute myeloid leukemia, Van Dyck et al. (2007) generated mice lacking PlagL2. The majority of these mice die of starvation within the first week after birth probably due to malabsorption of nutrients. This transcription factor is expressed in epithelial cells of the small intestine in the developing mouse embryo and in neonates. In PlagL2-deficient mice, the lamina propria, submucosal, and jejunal gut epithelial cells (enterocytes) were abnormal due to the accumulation of neutral lipids. Most affected were the interstitial space and the enterocytes of the distal jejunum where most of the lipids from the diet are absorbed. Thus, mice that lack PlagL2 display a defect in lipid absorption and their intestines contain high levels of triglycerides. Transmission electron microscopy revealed that enterocytes lacking PlagL2 assemble and secrete chylomicrons (large lipoprotein particles that are created from fat in the intestine), which are trapped in the gut interstitium. These particles are normally taken up by the lacteal capillary of the lymph system. Using oligonucleotide microarrays to compare changes in gene expression in the small intestines of wild-type and PlagL2-deficient mice, the authors found that a large fraction of genes with reduced expression patterns were involved in intracellular secretory transport, such as vacuolar sorting proteins and sorting nexins. This study implicates intracellular secretory pathways in lipid absorption in the gut, which should be examined further.
F. Van Dyck et al. (2007). Cell Metab. ***6****, 406–413.*

MIC-1 Makes You Lose Your Appetite

Anorexia and weight loss plague cancer patients in the late stages of the disease. Several cytokines have been implicated in causing this phenomenon. Johnen et al. (2007) now show that the cytokine MIC-1, a member of the TGF-β superfamily, is involved in cancer-induced anorexia and weight loss. The authors stably overexpressed MIC-1 in a human prostate cancer cell line DU145 and injected these cells into nude mice where they form tumors. Mice that had moderate or high levels of MIC-1 in their serum lost weight because they consumed 32% less food than control mice. Johnen et al. next examined patients with advanced prostate cancer who were experiencing weight loss and found that these patients had higher serum levels of MIC-1 than prostate cancer patients who were not losing weight and the serum levels of MIC-1 correlated with the degree of weight loss. The authors also examined patients with chronic renal failure, who often experience weight loss, and observed a correlation between high MIC-1 levels and low body mass index in these patients. Overexpression of MIC-1 in mice caused them to be smaller, eat less, and have less fat. The authors then determined that the arcuate and paraventricular nuclei of the hypothalamus may mediate the effects of MIC-1. In fact, selective overexpression of MIC-1 in the arcuate nucleus caused weight loss in mice, and this effect is probably mediated through hypothalamic TGF-β RII receptors and culminates in altered neuropeptide Y and α-MSH production, both of which are well-known regulators of food intake. MIC-1 and leptin (a key regulator of appetite and metabolism) both induce activation of the transcription factor STAT3 but in different group of neurons in the mouse brain, suggesting that they probably act in distinct pathways. MIC-1 appears to be an important regulator of appetite and controlling its levels could have implications for treating disease-associated anorexia and perhaps also obesity.
H. Johnen et al. (2007). Nat Med. ***13****, 1333–1340. Published online November 4, 2007. 10.1038/nm1677.*

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